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The role of clinical pulmonary infection score and some infection biomarkers in diagnosis and follow up in hospital acquired pneumonia

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ABSTRACT

Aims: Early diagnosis and treatment affect mortality in hospital-acquired pneumonia (HAP). Therefore, clinicians need some objective parameters for guiding treatment. The aim of this study was to determine the course of "clinical pulmonary infection score" (CPIS), C-reactive protein (CRP) and procalcitonin (PCT) in patients under treatment as well as the relationship of these parameters with each other and mortality.

Methods: This single-center, prospective, cross-sectional study focused on cases of HAP in hospitalized patients. In patients with HAP; CPIS, CRP and PCT assays were assessed on the first day. Appropriate treatment was initiated according to Turkish Thoracic Society HAP Task Force recommendations. On the 3rd day, CPIS evaluation and on the 4th day CRP and PCT analysis were repeated. All the patients' one month mortality rates were recorded.

Results: Among the 25 patients, there were 14 females. The mean age was 66±15 years. The mean duration for HAP development was 9.4±8.2 days. With a cutt-off value of 65 for age CPIS, CRP, PCT, length of hospital stay and mortality rate was not found different ($p>0.05$), however as the age increased HAP development duration significantly decreased ($r=-0.416$, $p=0.03$). We demonstrated a significant change between the first and the follow-up values of fever ($p=0.046$), leukocyte ($p<0.001$), PaO_2/FiO_2 ($p=0.016$), secretion presence ($p<0.001$), culture positivity ($p<0.001$) as well as total CPIS ($p=0.030$). However, there wasn't a significant difference in CRP and PCT levels. We couldn't show any relation between CPIS domains, total CPIS, CRP, PCT, HAP development duration and mortality rates.

Conclusion: Monitoring HAP treatment according to CPIS was found better than CRP and PCT. However, these parameters had no effect on mortality. For more accurate comments, studies with more patients are needed.

Keywords: C-reactive protein, clinical pulmonary infection score, hospital-acquired pneumonia, procalcitonin

INTRODUCTION

Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs either 48 hours after hospital admission, excluding cases within the incubation period upon admission, or within the 48 hours following discharge from the hospital.[1,2]

The microorganisms responsible for HAP, underlying conditions, risk factors, and pneumonia onset timing can vary. Despite being the second most common nosocomial infection, HAP has the highest mortality rate. Early and appropriate treatment significantly reduces mortality. Thus, prompt initiation of suitable empirical treatment following diagnostic sampling is crucial. Adjustments to antibiotic therapy based on sputum culture results can follow empiric treatment.

Specific infection markers have potential utility in both diagnosing and monitoring HAP.[3] A decline in initial C-reactive protein (CRP) levels over time is indicative of a positive prognosis. Notably, Procalcitonin (PCT) has been recognized as a valuable indicator for assessing both the diagnosis and prognosis of HAP.[3]

The Clinical Pulmonary Infection Score (CPIS) is a comprehensive tool used to diagnose Ventilator-Associated Pneumonia (VAP), a subset of HAP, and guide antibiotic treatment decisions. CPIS combines six clinical and laboratory parameters, including body temperature, white blood cell count, lung

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radiograph results, secretion presence, PaO_2/FiO_2 ratio, and sputum culture. The Turkish Thoracic Society (TTS) Adult Hospital-Acquired Pneumonia Diagnosis and Treatment Consensus Report emphasizes investigating CPIS's suitability for diagnosing and managing HAP, especially VAP, within the HAP context.[4]

METHODS

Study population

This single-center, prospective, cross-sectional study was conducted at a university hospital from January to November 2010. It focused on cases of HAP in hospitalized patients. HAP was diagnosed in patients who developed pneumonia 48 hours after admission, excluding cases with an incubation period at admission. Diagnostic criteria followed the Turkish Thoracic Society's guidelines, including new chest X-ray infiltrations and at least 2 of the following: fever>38°C, leukocytosis/leukopenia, purulent secretion, and reduced oxygenation. Participants included newly diagnosed, non-pregnant women, and individuals aged 18 and older. Data were collected from medical records of 25 participants. Those previously diagnosed with and treated for HAP were excluded.

The following factors: age, fever, white blood cell count, PaO_2/FiO_2 ratio, CRP, PCT, time to development of HAP and length of hospital stay were numerically divided into two groups for statistical group analysis.

- Age: < 65 years and ≥ 65 years
- Fever: < 38.4˚C and ≥ 38.4˚C,
- White blood cell count: < 11000 and ≥ 11000,
- PaO_2/FiO_2: < 240 and ≥ 240,
- CPIS: ≤6 and >6,
- CRP: <10.4 and ≥10.4,
- PCT: <0.05 and ≥0.05,
- Time to development of HAP: < 5 days and ≥ 5 days,
- Length of hospital stay: < 10 days and > 10 days

Other parameters were divided into two groups according to whether they were present in the patients or not.

Ethical Consideration

The study was carried out with the permission of the Scientific Research Evaluation and Ethics Committee of our university hospital (Date: 04/01/2010, Decision No: 0002). We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Outcome parameters

Initially, patient demographics were recorded, followed by medical histories and physical exams. Recorded parameters included body temperature, white blood cell count, sputum characteristics, lung X-ray results, PaO_2/FiO_2 ratio, CRP, and PCT levels. On day one, lower respiratory tract secretions were sent to the microbiology lab.

Peripheral blood samples in EDTA tubes were assessed for white blood cell count using the Beckman-Coulter laser system in the hematology lab. For CRP, blood samples were centrifuged for 5 minutes at 4000 rpm using a NUVE centrifuge, and the serum was analyzed via BN PROSPEC nephelometry. PCT values were determined using the ELFA method on the MIMIVIDAS device in the biochemistry lab.

For the determination of partial arterial oxygen pressure (PaO_2) value in the PaO_2/FiO_2 ratio, arterial blood samples were collected from the ulnar or femoral artery using a heparinized blood gas syringe. The samples were analyzed using the ion-selective method on the Roche Omni C Cobas b121 device in the biochemistry laboratory. The fractioned of inspired oxygen (FiO_2) value is a percentage value and shows the percentage of oxygen in the air that the patient has taken. For the FiO_2 value, if any oxygen replacement therapy was performed, the oxygen flow rates received by the patients were recorded in lt/min.

For stable patients, postero-anterior (PA) chest radiographs were taken with the patient in a standing position using the Trophy Radiology N500 HFS unit in the radiology department. Unstable patients who were unable to stand received anteroposterior (AP) chest radiographs using the SEDECAL SP-HF-40 mobile X-ray unit while lying down.

On the first day, respiratory secretion samples (sputum from non-intubated patients and endotracheal aspirate - ETA - from intubated patients) were collected and examined in the microbiology lab. Gram staining was used to assess quality and dominant microorganisms. Qualified sputum samples (≥25 leukocytes and ≤10 epithelial cells) were selected for microscopic examination. Bacteria were identified using standard microbiological techniques, with unidentified bacteria identified using BBL Crystal GP and Crystal E/NF ID kits or the BD Phoenix automated identification system.

In 1991, Pugin and colleagues developed the CPIS based on 6 clinical and laboratory data points, including fever, leukocyte count, presence and purulence of tracheal secretions, oxygenation, chest radiography findings, and positive or negative sputum culture (Table 1).[5] The total CPIS score is calculated by summing all the scores obtained by the patients according to the parameters in the table. Research has demonstrated a sensitivity and specificity of 93% and 96%, respectively, for pneumonia when CPIS>6.5 For this reason, we used a cut-off of 6 in our study.

Table 1. Clinical Pulmonary Infection Score (CPIS)[5]

Variables	Score 0	Score 1	Score 2
Temperature ˚C	≥36.5 and ≤38.4	≥38.5 and ≤38.9	≥39 or ≤36
Blood leukocytes µ/L	≥4000 and ≤11000	<4000 or >11000 *	
Tracheal secretions	None	Present, not purulent	Present, purulent
Oxygenation: PaO_2/FiO_2 mmHg	>240 or ARDS		<240 and not ARDS
Pulmonary radiography	No infiltration	Diffuse or patchy infiltrate	Localized infiltrate
Culture of tracheal aspirate	Pathogenic bacteria cultured ≤ 1 or no growth	Pathogenic bacteria cultured > 1**	

*: band forms ≥ 500=+ 1 point, **: same pathogenic bacteria seen on the Gram stain=+ 1 point

After the initial assessment, the total CPIS was calculated based on data including fever, white blood cell count, PaO_2/FiO_2, chest X-ray findings, secretion characteristics and microbiological culture results and empirical antibiotic treatment was initiated according to the recommendations of the guidelines. On the third day of treatment, the patients' body temperatures, white blood cell counts, secretion characteristics, PaO_2/FiO_2 values and chest radiograph findings were re-evaluated. To investigate the presence of microbiological growth, another secretion sample was collected. On the fourth day, only hs-CRP and PCT levels were checked again.

Patients were then followed until discharge and their health status was monitored. Patients were re-evaluated during the first month after diagnosis. If patients were discharged within one month of HAP diagnosis, they were contacted by telephone for assessment. Alternatively, if patients were still being in hospital during the first month after HAP diagnosis, they were assessed at the bedside to collect information on their health status.

Statistical Analysis

Following the collection of data from 25 patients, statistical analysis was conducted. For parametric variables, the Student's t test was used for dependent groups and for non-parametric variables the Wilcoxon test was used. Non-parametric correlations were analysed using the Spearman correlation test. To determine mortality rates within the groups and compare other ratios, the Chi-square test and Fisher's exact test were employed. Values with $p<0.05$ were considered statistically significant.

RESULTS

Out of the 25 patients included in the study, 14 (56%) were female. The mean age was 65.6 ± 15.16 years. Of the patients, 13 (52%) were hospitalized in the general ward, while 12 (48%) were under intensive care unit monitoring and treatment. Among them, 24 (96%) were admitted to internal medicine departments or intensive care units, and only 1 patient (4%) was in the intensive care unit of the surgical clinic.

When examining the comorbid diseases of the patients, diabetes mellitus (DM) was present in 1 (4%) patient, cardiovascular disease in 4 (16%) patients, structural lung disease (bronchiectasis) in 1 (4%) patient, chronic obstructive pulmonary disease (COPD) in 9 (36%) patients, chronic kidney disease in 2 (8%) patients, neurological disease in 12 (48%) patients, malignancy in 3 (12%) patients, and a history of respiratory failure in 5 (20%) patients.

The time interval from hospital admission to the development of HAP was analyzed for all patients, with an average of 9.4 ± 8.2 days. This interval was 4 days or earlier for 11 (44%) patients, and 5 days or later for 14 (56%) patients.

Table 2 displays the age, gender, some laboratory values, initial and follow-up data, and one-month mortality information for all cases.

Table 2. Age, gender, some laboratory values, and mortality information of the cases

			Initial			Follow-up			
No	Age	Gender	CPIS	CRP	PCT	CPIS	CRP	PCT	1-month mortality
1	24	F	8	7.20	0.15	8	6.59	0.05	Surviving
2	75	F	1	20.60	0.14	1	-	0.05	Surviving
3	57	F	5	20.60	37.83	3	8.49	0.39	Surviving
4	65	F	3	8.28	0.46	3	3.60	0.74	Surviving
5	63	F	6	0.50	0.31	3	0.50	0.05	Surviving
6	27	F	4	31.20	0.05	4	11.20	0.05	Surviving
7	77	M	4	10.30	0.05	2	10.30	0.06	Surviving
8	83	F	8	10.30	0.12	7	10.30	0.23	Surviving
9	65	M	5	10.30	1.17	5	10.30	4.19	Surviving
10	54	M	5	10.30	1.20	3	10.30	0.95	Surviving
11	55	F	6	-	0.11	6	10.30	0.06	Exitus
12	70	M	4	4.41	0.58	2	10.30	0.42	Surviving
13	55	M	5	4.46	0.39	2	4.33	0.05	Surviving
14	77	M	8	10.30	0.37	7	10.30	0.82	Surviving
15	68	M	5	10.30	12.76	5	10.30	97.99	Surviving
16	85	F	5	10.30	0.05	3	10.30	0.05	Surviving
17	82	F	5	10.30	0.27	3	10.30	0.06	Exitus
18	62	M	7	10.40	1.98	5	10.40	0.66	Surviving
19	80	F	3	10.40	0.29	3	10.40	0.14	Surviving
20	75	M	8	10.40	7.46	4	10.40	0.32	Surviving
21	81	F	5	10.40	0.08	1	10.40	0.08	Exitus
22	55	M	6	10.40	0.06	6	10.40	0.05	Exitus
23	65	F	7	10.40	38.00	10	10.40	16.65	Surviving
24	63	M	7	10.40	2.99	3	10.40	3.33	Surviving
25	67	F	8	10.10	35.80	4	5.25	23.80	Exitus

CPIS, clinical pulmonary infection score; CRP, C-reactive protein; F, female; PCT, procalcitonin; M, male.

Considering the wide age range of the patients in the study, ranging from 24 to 85, they were divided into two groups: those under 65 and those aged 65 and above. The relationship between these groups and parameters such as CPIS, CRP, PCT values, time to HAP development, length of hospital stay, and 1-month mortality rates were examined. In this analysis of age being categorized as under 65 and 65 and above, no significant relationship was found between any parameter and the time to HAP development.

Furthermore, we aimed to investigate the relationship between the 2 most common comorbid diseases and CPIS, CRP, PCT values, time to HAP development, length of hospital stay, and 1-month mortality rates. No significant differences were found based on the presence of COPD or neurological diseases in relation to these parameters.

The means and p-values of the 6 CPIS parameters at the beginning and follow-up are shown in Table 3. Among these parameters, fever, white blood cell count, PaO_2/FiO_2 ratio, microbiological growth, and secretion data demonstrated statistically significant changes between initial and follow-up measurements. Only X-ray findings did not exhibit statistically significant changes. During follow-up, improvements were observed in body temperature, white blood cell count, presence and purulence of secretion, while an increase was observed in PaO_2/FiO_2 values and microbiological growth rates.

Table 3 Changes in CPIS parameters at baseline and follow-up

CPIS parameters		Initial	Follow-up	p value
Fever (Mean ± SD)		37.06±1.05	36.7±0.62	0.046*
Leukocyte Median (IQR)		15160 (11980-17800)	11250 (8150-14620)	0.001*
PaO_2/FiO_2 Median (IQR)		210(152-230)	265(205-310)	0.016*
Secretion (%)	Absent	6 (%24)	9 (%36)	0.001*
	Present. not purulent	4 (%16)	6 (%24)	
	Present. purulent	15 (%60)	10 (%40)	
Infiltration on chest radiograph n (%)	Present	19 (%76)	19 (%76)	>0.05
	Absent	6 (%24)	6 (%24)	
Microbiological growth n (%)	Present	7 (%28)	9 (%36)	0.01*
	Absent	18 (%72)	16 (%64)	

CPIS, clinical pulmonary infection score; n, number.

The PaO_2/FiO_2 ratio was found to have the most significant impact on the initial CPIS value among the six parameters studied (p=0.024 ve r=-0.45). No significant relationship was observed with the other parameters. In terms of microbiological examination, 28% of the patients had growth in their lower respiratory tract secretion samples at the time of diagnosis. However, this increased to 36% in the follow-up sample collected on the third day. Of the patients, 12% had *Pseudomonas aeruginosa* growth both at diagnosis and in the follow-up sample, and the same was observed for Acinetobacter spp. in another 12% of patients. In 12% of patients, there was no growth in the secretion on the first day, but Acinetobacter spp. was only grown in the follow-up. Only one patient had *Staphylococcus aureus* growth at the time of diagnosis, which did not persist in the follow-up sample. Additionally, a statistically significant difference in the CPIS value was found between patients with growth and those without (Table 4).

Table 4. Relationship between the presence of sputum bacterial growth and CPIS value

		CPIS		Total	p value
		≤ 6 n (%)	> 6 n (%)		
Microbiological Growth	Present	2 (%29)	5 (%71)	7 (%28)	0.008*
	Absent	15 (%83)	3 (%17)	18 (%72)	
Total		17 (%68)	8 (%32)	25 (%100)	

CPIS, clinical pulmonary infection score; n, number.

No statistically significant difference was found between the baseline and follow-up values of CRP and PCT, whereas a statistically significant difference was found between CPIS at diagnosis and CPIS at follow-up (Table 5). In addition, when the baseline and follow-up values of CPIS and the baseline and follow-up values of these 2 inflammation markers were analysed among themselves, no statistically significant difference was found between the baseline CPIS value and baseline CRP, baseline PCT values and between the follow-up CPIS and follow-up CRP, follow-up PCT values (Table 6).

Table 5. Changes in CPIS, CRP, PCT values at follow-up compared to baseline

	Initial	Follow-up	p value
CPIS (Mean±SD)	5.52±1.82	4.12±2.22	0.030*
CRP (Median±IQR)	10.30 – 10.10/10.40	10.30 – 8.90/10.40	0.128
PCT (Median±IQR)	0.37- 0.12/2.49	0.23 – 0.05/0.89	0.200

CPIS, clinical pulmonary infection score; CRP, C-reactive protein; PCT, procalcitonin; SD, Standard deviation; IQR, Interquartile range.

Table 6. The relationship of CPIS at diagnosis (A) with initial CRP, PCT values and at follow-up (B) CPIS with follow-up CRP, PCT values

A	Initial CPIS	B	Follow-up CPIS
Initial CRP	p= 0.563 r= - 0.124	Follow-up CRP	p= 0.473 r= 0.154
Initial PCT	p= 0.156 r= 0.292	Follow-up PCT	p= 0.204 r= 0.263

CPIS, clinical pulmonary infection score; CRP, C-reactive protein; PCT, procalcitonin.

When the factors affecting the time to development of HAP were investigated, only a statistically significant correlation was found between age and the time to development of HAP, and the time to development of HAP was shorter with increasing age. Apart from age, no significant correlation was found between fever, leukocyte, PaO_2/FiO_2 value, presence of COPD, CPIS value, baseline CRP, PCT levels and duration of hospitalization and the time to develop HAP (Table 7).

In our study, the patients were divided into 2 groups with a hospitalization period of less than 10 days and more than 10 days, and the relationship between age, fever, leukocyte, PaO_2/FiO_2, presence of secretion, lung radiography findings, CPIS, CRP, PCT values and the duration of HAP development was analysed. In this analysis in which all parameters were grouped according to certain threshold values, no statistically significant relation was found between any parameter and the duration of hospitalization. Only CRP level was found to be higher, although not statistically significant, in patients who were hospitalized for a long time

(more than 10 days). Finally, the association of 1-month mortality rates with 6 CPIS parameters, total CPIS value, CRP, PCT, duration of HAP development, presence of COPD and presence of Acinetobacter spp. was analysed, and none of these parameters were found to be significantly associated with 1-month mortality.

Table 7. Relationship between some demographic, clinical and laboratory data and the development time of HAP

Baseline data	Association with HAP development time (p and r values)
Age	p= 0.03* and r= -0.416*
Body temperature	p= 0.859 and r= -0.038
Leukocyte count	p= 0.632 and r= -0.101
PaO_2/FiO_2	p= 0.495 and r= 0.143
Presence of COPD	p= 0.087 and r= 0.280
CPIS	p= 0.210 and r= -0.260
CRP	p= 0.198 and r= 0.273
PCT	p= 0.295 and r= -0.137
Length of hospital stay	p= 1.0 and r= 0.242

COPD, chronic obstructive pulmonary disease; CPIS, clinical pulmonary infection score; CRP, C-reactive protein; HAP, hospital acquired pneumonia; PCT, procalcitonin.

DISCUSSION

This study aimed to evaluate the use of the CPIS clinical scoring system, CRP and PCT biomarkers in monitoring HAP treatment and their relationship with each other and short-term mortality rate. No significant correlation was found between patient demographics, biomarker levels, and mortality rates. However, improvements in fever, leukocyte count, secretion quality, and CPIS values were observed with antibiotic treatment.

HAP is a leading cause of mortality in hospital-acquired infections. In Turkey, the frequency of HAP has been reported to be 15-22%, but it varies depending on the clinic where the patient is hospitalized.[6] Patients treated in intensive care units are at a higher risk of developing HAP, with the incidence being 5-10 times higher compared to other patients. In a study conducted in Turkey, this rate reached 20 times higher in intensive care unit patients.[6] The possibility of recto-pulmonary contamination and colonization leading to HAP is high in patients in need of care and those in intensive care units. The risk factors for developing HAP include patient-related factors, infection control factors, medical interventions during hospitalization, and the infectious agent. Advanced age is one of the patient-related factors that contribute to higher rates of HAP and increased mortality. Some authors correlate the high incidence of pneumonia in elderly people with the presence of comorbid diseases and longer hospital stays rather than chronological age.[7] However, age is still an important risk factor in patients with non-ventilated HAP, which is thought to be due to some physiological and immunological changes resulting from the aging process.[8]

Apart from age, there are several risk factors specific to the development of HAP, increased mortality and the development of disease with multidrug-resistant pathogens.[9,10] A study conducted by Fortaleza identified age over 65, antacid use, and central nervous system (CNS) diseases as risk factors for healthcare-associated pneumonia.[8] Another study by Dandagi listed mechanical ventilation, prolonged coma or decreased level of consciousness, supine position, aspiration, comorbid diseases, hospitalization diagnosis, prolonged intensive care unit stay, use of positive end-expiratory pressure during mechanical ventilation, severe disease status, multiple organ dysfunction, advanced age, malnutrition, use of nasogastric tube, use of paralytic agents, use of antacids, male gender, enteral nutrition, and immunosuppression as risk factors for nosocomial pneumonia.[11] Gastmeier's study found age, gender, duration of hospitalization, type and size of hospital, intubation, and the use of central venous catheter as risk factors for nosocomial pneumonia-related death.[12] In our study, it was observed that 60% of patients who died in the one-month follow-up were over 65 years old, but due to the small number of patients, no statistically significant difference was found in relation to advanced age and mortality.

Chronic and comorbid conditions including cancer, COPD, chronic lung diseases, heart diseases, and renal failure impact infection progression in HAP and VAP patients.[13] Effective VAP treatment depends on microbial diagnosis, accurate antibiotics, comorbidities, patient response, and organ function.[14] In a 7-year Vallés study on HAP, poor prognosis linked to septic shock with specific microorganisms and COPD.[15] Deng's research identified risk factors for elderly HAP development, including intensive care unit admission, extended COPD history, immunosuppression, antibiotics, mechanical ventilation, and CNS disease.[16] Our study indicated COPD patients had shorter HAP development and longer hospital stays, aligning with literature.

Central nervous system diseases compromise cough and swallowing reflex, facilitating microorganism entry into the lower respiratory tract,[17] especially risky for non-ventilated HAP.[8] A randomized study with 563 patients revealed advanced age, prolonged mechanical ventilation, neurological disease, and low PaO_2/FiO_2 ratio at the 3rd day as risk factors for clinical decline.[18] In our study, 12 patients (48%) had prior neurological diseases. Of them, 7 (58%) had early HAP development, and 9 (75%) stayed in hospitals over 10 days. Neurological disease correlated with HAP onset and extended hospital stays, while did not affect mortality significantly, possibly due to limited patient numbers. Disease severity and risky conditions in non-neurological patients might explain the mortality outcome.

Diagnosing HAP in patients with comorbid diseases can be challenging. To help with diagnosis and treatment guidance, the use of CPIS, a clinical scoring system primarily used for VAP, is recommended. CPIS scores above 6 in VAP patients can indicate a higher likelihood of pneumonia. The main purpose of CPIS is to evaluate and guide treatment. In Luna's study, the change in CPIS values over the first and third days was analyzed in patients with clinical and bacteriological confirmed VAP.[19] The study found that CPIS values gradually decreased during follow-up, with a more significant decrease in surviving patients compared to non-surviving patients. Lower mortality rates were observed in patients with CPIS values below 6 on the third or fifth day after VAP onset. Another study investigated the contribution of CPIS in the treatment of suspected pneumonia in intensive care patients.[20] CPIS was used as a decision-making factor for starting or terminating antibiotic treatment, however, it was discovered that 42% of patients diagnosed with pneumonia by clinicians had CPIS values of 6 or less on the first day. Today, CPIS is still used to manage the antibiotic treatment. In a quasi-experimental study, integrating procalcitonin and

CPIS reduced inappropriate antibiotics for severe Coronavirus disease 2019 (COVID-19) cases, but not for moderate ones.[21] In our study, HAP was not diagnosed according to CPIS, and there were 17 (68%) patients with an initial CPIS of 6 or less and 29% of these patients had microbiological growth. These findings suggest that CPIS alone is not as useful a marker for the diagnosis of HAP as hoped, and this is supported by the literature. In our study, when each parameter was analysed individually in the CPIS values at the beginning of treatment and on the 3rd day of treatment, significant improvement was observed with treatment in terms of fever, leukocytes, PaO_2/FiO_2 and presence of secretion. In addition, PaO_2/FiO_2 ratio was found to be the most effective parameter among 6 parameters on the initial CPIS value. In terms of the presence of infiltration on chest radiography, no change was observed at the beginning of treatment and at the control. This finding is compatible with the general knowledge that the response to treatment is primarily clinical, followed by radiological improvement. However, in terms of microbiological growth, there was an increase in the number of patients with growth in the control compared to the first day. These findings support the more appropriate use of CPIS in HAP treatment follow-up.

In intensive care units (ICUs) worldwide, infections significantly contribute to morbidity and mortality. Vincent et al.[22] conducted a one-day study on 13,796 patients, finding 51% infected and 71% on antibiotics. Respiratory infections constituted 64%, with positive cultures in 70% of cases. Longer ICU stays correlated with higher infection rates, especially for drug-resistant bacteria (Methicillin-resistant *Staphylococcus aureus*, *Acinetobacter*, *Pseudomonas* spp. and *Candida* spp.). Infected patients had more than twice the ICU mortality (25% vs. 11%) and hospital mortality (33% vs. 15%) compared to non-infected patients.[22] In our study, only 28% of patients showed microbiological culture positivity at diagnosis, including *Pseudomonas aeruginosa, Acinetobacter* spp., and *Staphylococcus aureus*. No statistically significant links were found between culture positivity and hospitalization duration or 1-month mortality rate. This could be due to limited cases and growth instances, and potential issues during sample collection and transport. Most patients being followed outside chest diseases clinics might contribute.

Many studies have been conducted to compare CRP with PCT in clinical practice. Simon discovered that PCT levels were more sensitive (88% vs 75%) and specific (81% vs 67%) than CRP in discriminating bacterial inflammation from noninfectious sources of inflammation in adults in a meta-analysis of 12 investigations.[23] Holm demonstrated that while PCT was not superior to CRP in detecting individuals with pneumonia, it was superior to CRP in distinguishing Mycoplasma pneumoniae from other bacterial diseases.[24] In our study, no significant change was seen between CRP and PCT values at baseline and follow-up, however there was a decrease in PCT values that did not achieve statistical significance.

PCT is a serum biomarker that has showed efficacy in distinguishing between viral and bacterial infections, and is frequently utilized in critically sick patients as a guide to antibiotic de-escalation/discontinuation.[25] CRP is an acute-phase inflammatory protein, also plays a key role in identifying and evaluating bacterial infections.[25] However, it is known that the use of both alone is not fully adequate for diagnosis, treatment decision-making, or prediction of morbidity and mortality. As a result, composite biomarkers with high accessibility, such as the combination of neutrophil/lymphocyte count ratio, CRP, and leukocyte count may assist in early diagnosis and severity assessments. So, there are studies in the literature that evaluated CPIS, CRP and PCT together. In a study of 20 suspected VAP patients PCT, CRP and CPIS values were evaluated intermittently.[26] Patients with a microbiologically verified diagnosis of VAP had a higher PCT value than those without a documented diagnosis. PCT had the highest sensitivity and specificity (78% and 97%, respectively), CPIS showed the same sensitivity but lower specificity (80%), whereas CRP had the lowest sensitivity (56%) but comparatively higher specificity (91%). In the end, when PCT levels below the threshold values are paired with CPIS, the rate of false positivity in the diagnosis of VAP is reduced.[26] In our study, no significant difference was found between baseline and follow-up CPIS, CRP and PCT parameters in terms of sensitivity and specificity values to support the diagnosis of HAP, and no statistically significant result was found when the relationship between CPIS, CRP and PCT was analyzed. However, when all parameters were evaluated alone, a statistically significant difference was found in the follow-up values of fever, leukocytes, PaO_2/FiO_2, secretion, microbiological growth and CPIS compared to the baseline values. This result supports that clinical parameters are more useful in follow-up than laboratory data such as CRP and PCT. The fact that PCT values decreased after treatment, although not significantly, suggests that CRP is the least recommended parameter to be used in follow-up.

Long hospitalization is a risk factor for HAP, which can increase the duration of hospitalization, treatment costs, and mortality. Elderly patients are particularly vulnerable to complications associated with hospitalization, such as nosocomial infections, loss of function, immobility, and confusion. Pneumonia and urinary tract infections are the most common nosocomial infections.[27] In our study we found that only CRP levels were significantly higher in patients with long hospital stays, but no significant relationships were found between other parameters and duration of hospitalization. The main reason for prolonged hospitalization was the primary diagnosis and underlying diseases of the patients. In a study PCT, CRP, and clinical scores (CPIS, etc) were compared in patients with healthcare-associated infections, and it was found that the increase in PCT, CRP, and clinical score levels were correlated with mortality rates.[3] In contrast, in our study, lower CRP level was not associated with 1-month mortality, but the CRP and PCT levels remained elevated in most patients who died within 1 month.

Study Limitations

The most prominent limitation of our study is that it is a single-centre study with a small number of participants. Some patients did not provide sufficient and high-quality lower respiratory tract samples, such as sputum, particularly on the initial day of HAP diagnosis. Finally, the fact that some of the patients were hospitalized in clinics other than Chest Diseases may also have had a negative impact on sample collection.

CONCLUSION

As a result of our study, when the CPIS clinical scoring system and PCT and CRP biomarkers were examined in terms of monitoring HAP therapy, the most relevant parameter

to be employed in monitoring was determined to be CPIS. PCT came in second, whereas CRP was not determined to be an acceptable marker for follow-up. No parameter was found to be useful in predicting mortality. However, further investigations on more instances are needed to establish more certain conclusions.

ETHICAL DECLARATION

Ethics Committee Approval: The study was carried out with the permission of Ethical Committe of Manisa Clinical Researches (Date:04.01.2010, Decision No: 0002).

Informed Consent: All patients voluntarily signed the informed consent form.

Reviewer Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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